Institution: The University of Warwick

Unit of Assessment: B8 Chemistry

Title of case study: Wills Catalysts: commercialised systems for enantioselective production of pharmaceutical intermediates

1. Summary of the impact

A process for the commercial production of a family of Warwick-invented organometallic catalysts has been developed and patented by Johnson Matthey (JM). The catalysts – which have been sold internationally to several fine chemical and pharmaceutical companies in kilogram quantities, capable of producing tonnes of product – are in widespread industrial use for synthesis and scale-up. Other companies have protected, and are marketing, similar 'copycat' catalysts. JM continues to work in collaboration with Warwick Chemistry on the next generation of catalysts.

2. Underpinning research

In the mid-1990s, R. Noyori (Nagoya, Japan) reported a series of ruthenium-based catalysts containing an arene and chiral diamine that demonstrated high reactivity and selectivity for the asymmetric reduction of ketones to alcohols – versatile intermediates in pharmaceutical manufacture. At Warwick, Professor Martin Wills and his research team have been carrying out research in the area of asymmetric reduction using organometallic catalysts, with a focus on their applications, as described in over 40 publications since 1997. A major project carried out as part of this research was directed at the development of improved variants of the 'Noyori catalysts'. The resulting 'Wills catalysts' [1-6] have substantially higher activity, use lower catalyst loadings and cause fewer side reactions. This reduces cost, waste and energy usage.

In 2004, Wills was awarded the first of three EPSRC grants to support his research in this area [7–9]. This led to the development of a series of novel Ru(II)-based catalysts, in which a covalent tether from the chiral diamine component to the η^6-arene unit was incorporated. This tether – the essential motif of the Wills catalyst family – provides conformational and chemical stability as well as the unprecedented potential to create derivatives with a predictable structure. Wills established the principle of tethering in this system in 2004 [1], and systems with exceptional activity and versatility were reported in 2005 [2]. The tethering concept was further extended to analogous Rh catalysts [3].

Wills and his group further developed the new Ru(II) tethered catalysts, and reported their mechanisms and wider applications in the following years (11 additional papers). In particular, the research resulted in the development of a catalyst for the reduction of a wide range of ketone substrates to alcohols under transfer-hydrogenation conditions (formic acid being the most commonly used source of hydrogen) [4,5], and later to the extension of the catalyst to pressure-hydrogenation reactions (where hydrogen gas is used as the reducing agent) [6]. It was this class of highly engineered catalysts that led to the enhanced reaction rates and increased compatibility needed for the key substrate classes used in industry. These include α-chloroacetophenones and 2-ketopyridines (which are prone to side reactions leading to catalyst deactivation), and highly hindered substrates (which are normally unreactive).

3. References to the research

[1] *A New Class of 'Tethered' Ruthenium(II) Catalysts for Asymmetric Transfer Hydrogenation Reactions*, J. Hannedouche, G. J. Clarkson and M. Wills; *J. Am. Chem. Soc*. **2004**, *126*, 986–987, DOI: 10.1021/ja0392768.

[2] *A Class of Ruthenium(II) catalyst for Asymmetric Transfer Hydrogenations of Ketones*; A. M. Hayes, D. J. Morris, G. J. Clarkson and M. Wills; *J. Am. Chem. Soc*. **2005**, *127*, 7318–7319, DOI: 10.1021/ja051486s.

[3] *A Stereochemically Well-Defined Rhodium(III) Catalyst for Asymmetric Transfer Hydrogenation of Ketones*, D. S. Matharu, D. J. Morris, A. M. Kawamoto, G. J. Clarkson, and M. Wills; *Org. Lett.* **2005**, *7*, 5489–5491, DOI: 10.1021/ol052559f.

[4] *An Unexpected Directing Effect in the Asymmetric Transfer Hydrogenation of α,α-Disubstituted Ketones*; R. Soni, J.-M. Collinson, G. J. Clarkson and M. Wills; *Org. Lett.* **2011**, *13*, 4304–4307, DOI: 10.1021/ol201643v.

[5] *An investigation into the tether length and substitution pattern of arene-substituted complexes for asymmetric transfer hydrogenation of ketones*, F. K. Cheung, C. Lin, F. Minissi, A. L. Crivillé, M. A. Graham, D. J. Fox and M. Wills, *Org. Lett.* **2007**, *9*, 4659–4662, DOI: 10.1021/ol702226j.

[6] *Application of Tethered Ruthenium Catalysts to Asymmetric Hydrogenation of ketones, and the Selective Hydrogenation of Aldehydes*, K. E. Jolley, A. Zanotti-Gerosa F. Hancock, A. Dyke, D. M. Grainger, J. A. Medlock, H. G. Nedden, J. J. M. Le Paih, S. J. Roseblade, A. Seger, V. Sivakumar, I. Prokes, D. J Morris and M. Wills; *Adv. Synth. Catal.* **2012**, *354*, 2545–2555, DOI: 10.1002/adsc.201200362.

Research Council Grants

[7] *Stereochemically Well-Defined Ruthenium(II) Catalysts For Asymmetric Transfer Hydrogenation*; EPSRC GR/S72214/01, Jul 2004 – Dec 2007, £183,371, M Wills.

[8] *Asymmetric Transfer Hydrogenation Using Tethered Ligands*; EPSRC EP/D031168/1, Jan 2006 – Mar 2009, £186,531, M. Wills.

[9] *Asymmetric Transfer Hydrogenation of Imines*; EPSRC EP/F019424/1, Jan 2008 – Mar 2011; £301,135; M. Wills.

4. Details of the impact

Catalytic hydrogenation is a pivotal chemical transformation which underpins the synthesis of numerous high-value target molecules, materials and intermediates. Wills tethered catalysts – invented at Warwick and commercialized by collaborators and competitor businesses – have been shown to have significant commercial advantages over the Noyori system. A rapidly growing number of impacts are reported here with commercial catalyst producers, suppliers and pharmaceutical companies in several countries.

Commercialisation of the 'tethered' catalysts by Johnson Matthey

The Wills catalyst was tested by Johnson Matthey Catalysis and Chiral Technologies (JM CCT) and the system "emerged […] as the only transfer hydrogenation catalysts providing activity on the difficult substrate under study" and offering "remarkably increased activity when compared to previous generations of catalysts while retaining high enantioselectivity" [10]. A team of nine inventors worked at JM CCT on a scalable synthetic route to the catalysts, which was later demonstrated on multi-100s gram scale and kg-scale at Alfa Aesar; a Johnson Matthey company [10]. A patent was filed in 2009 [11].

Since 2009 JM CCT – through Alfa Aesar, SigmaAldrich and Strem – has sold four Wills tethered catalysts in the family, either individually or as a part of a 'kit' (catalogue prices £368–£560 per gram). JM CCT also uses the material in collaborative projects with client companies worldwide [10].

While specific details of JM CCT customers and sales are confidential, they state that Wills catalysts have been made (2009 - June 2013) "on multi Kg scale for several international customers involved in the production of pharmaceutical intermediates" [10]. JM CCT also states that "1 kg of catalyst may be sufficient for making tonnes of a particular target" [10]. The catalysts are used in large scale processes.

Use of Wills catalysts by pharmaceutical companies in research, scale-up and production

A large number of pharmaceutical and related companies have used the catalysts in the synthesis of target molecules, as evidenced below, with several quoting the use of the JM CCT supplier, and all describing specific Wills catalysts or directly citing Wills papers. The Wills catalyst system is readily available and easy to apply. Enantioselectivity, functional group tolerance and catalyst stability are all more favourable than in the untethered Noyori system. Hence, there has been rapid take-up of the catalysts by industry. The examples below almost certainly represent a small proportion of the number of actual uses, patents, and the economic and healthcare impacts of the Warwick research.

- AstraZeneca (Sweden & UK), one of the largest pharmaceutical companies in the world, describes in a process patent the use of (*S*,*S*)-teth-TsDpen-RuCl (a JM CCT trade name for a Wills catalyst) in the catalytic asymmetric synthesis of a class of anti-asthmatic bronchodilator drugs [12].
- Synthon BV (Netherlands) report the use of a Wills catalyst in the key chirality-inducing reduction step in their synthesis of the anti-asthmatic drug montelukast (singulair), a drug which in 2010 was the fourth most prescribed drug in the US (24.7 M). They conclude, "It has now been discovered that the use of [Wills catalyst] can provide a more suitable process for the asymmetric transfer hydrogenation reaction" [13].
- Archimica GMBH (Germany) patented the use of a Wills tethered catalyst in the key chirality-generating step of their synthesis of the third generation antiepileptic drug Eslicarbazepine [14].
- Boehringer Ingelheim (Germany), one of the largest pharmaceutical companies in the world, describe their route to certain chemokine inhibitors via the reduction of an early-stage intermediate using a Wills tethered catalyst [15].
- Lek Pharmaceuticals (Slovenia), part of the Sandoz group, has reported an improved process for the preparation of intermediates on route to non-steroidal selective estrogen receptor modulators such as lasofoxifene using the Wills catalyst [16].
- In collaboration with Eli Lilly (USA), one of the largest pharmaceutical companies in the world, JM CCT have developed an achiral version of the Wills tethered catalysts and have applied this to racemic reductions [10].

Additional examples from a rapidly growing list further demonstrate the international commercial reach of the Wills catalysts, in e.g. China (Hunan Fangsheng Pharma, patent CN102978253A), USA (Ambit Biosciences, patent US2012053193A1) and Italy (Zach Systems/Zambon Chemicals, patent WO2012120086).

Commercialisation of Wills tether catalysts by others

With Dr Reddys Ltd (DRL), the Wills group investigated the development of a further class of tethered catalyst containing an ether linkage (2007-11) [17]. At this time another industrial lab (Takasago, Japan) disclosed work on this specific variant [18] and this tethered catalyst has subsequently been commercialised by Takasago under the trade name DENEB [19]. A representative of DRL notes in respect of this commercialisation, "Takasago have clearly invested a great deal of funding in DENEB" [17].

Further companies have developed catalysts that use the Wills tether concept: a nitrogen atom tether system was reported by PhosPhoenix SARL researchers (*Org. Lett.* **2013**, *15*, 1614–1617); a polymer-supported version of a Wills tethered catalysts was commercialised by PolyAn [20].

Continuing research at Warwick and commercial collaboration with JM CCT

JM CCT recognized the commercial need for the use of dihydrogen as the primary reducing agent and will develop this area with Wills through a TSB-funded collaborative grant *Development of the future generation of catalysts for asymmetric reduction* (TSB ref: 101330, Mar 2013, £216k plus £108K from JM CCT), extending the range of catalysts and their applications. In a further development, a new synthetic route to the Wills catalysts and novel variants is the subject of a patent application filed by Warwick (UK patent application 1219716.6, 02 Nov 2012; PCT/GB2013/05286901, 01 Nov 2013); licensing negotiations are ongoing.

The Wills catalyst class has thus had very significant impact in a critical chemical transformation practised very frequently in a major global industry and leading to high value products on a large scale. The Warwick research also underpinned the development and commercialisation of competitor catalysts of the same essential design. As noted by JM CCT, Warwick Chemistry has, "provided modern catalysis with a truly powerful synthetic tool".

5. Sources to corroborate the impact

[10] Johnson Matthey, Catalysis and Chiral Technologies; statement 17 June 2013.

[11] Process patent WO2010106364A2 (Johnson Matthey, priority date 17 Mar 2009), web link.

[12] Process patent WO2012156693A1, *Processes for the preparation of the compound of formula (II) and intermediate compounds for use in the processes* (AstraZeneca Ab and AstraZeneca UK Ltd, priority date 13 May 2011), web link.

[13] Process patent WO2009130056A1, *Process for making montelukast intermediates* (Synthon BV., priority date Apr 25, 2008), web link.

[14] Process patent WO2011131315A1, *Process for the asymmetric transfer hydrogenation of ketones* (Archimica GMBH, priority date 23 Apr 2010), web link.

[15] Patent US20130217728, *New CCR2 Antagonists* (Boehringer Ingelheim International GMBH, priority date 01 June 2010), web link.

[16] Patent EP2644603A1, *Synthetic route for the preparation of substituted 2-phenyl-1,2,3,4-tetrahydronaphthalene-1-ols* (LEK Pharmaceuticals d.d., priority date 30 Mar 2012), web link.

[17] Dr Reddy's, Chirotech Technology Ltd; statement 13 Aug 2013.

[18] Patent WO 2012/026201 *Ruthenium-diamine complexes and method for producing optically active compounds* (Tagasago Int. Corporation, priority date 01 Aug 2010), web link. See also *J. Am. Chem. Soc.* **2011**, *133*, 14960–14963, DOI: 10.1021/ja207283t.

[19] Takasago website and presentation on DENEB, retrieved 11 Sept 2013 from web link or available on request.

[20] PolyAn catalogue entry for heterogenised Wills catalyst, retrieved 31 July 2013 from web link or available on request. See also *Adv. Synth. Catal.* 2010, **352**, 2497-2506, DOI: 10.1002/adsc.201000340